REMARKS

Status of the Claims

Claims 1-41 are pending. Claims 1-7, 12,13, 18, 19, 22-31 and 34-41 are withdrawn. Claims 8-11, 14-17, 20-21 and 32-33 stand rejected. Claims 1-7, 12, 13, 18, 19, 22-31 and 34-41 are canceled herein. Claims 8, 14, 15, 20, 21 and 32 are amended and claims 10, 11, 16, 17 and 33 are canceled herein. No new matter is added to the amended claims.

Claim Amendments

Claims 10 and 11 are canceled and their limitations are incorporated in Claim 8, which is amended to overcome the 35 U.S.C §112, second paragraph and first paragraph (enablement and written description requirement) and 35 U.S.C. §102(b) rejections. Amended claim 8 is directed to a method of inhibiting cell-cell interaction. Such a method comprises contacting the cells with an antibody directed against a peptide with a sequence of SEQ ID No. 41 or SEQ ID No. 2 that is derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP). This contact with the antibody blocks binding of integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP), thereby inhibiting the cell-cell interaction.

Claims 16 and 17 are canceled and their limitations are incorporated in claim 15, which is amended to overcome the 35 U.S.C. first paragraph (enablement and written description requirement), 35 U.S.C. §102(b) and 35 U.S.C. 103 rejections. Amended claim 15 is directed to a method of treating a patient with a pathological condition related to an integrin-mediated cell-cell interaction. Such a method comprises administering to the patient an antibody directed against a peptide with a sequence of SEQ ID No. 41 or SEQ ID No. 2 that is derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP), where the antibody blocks binding of

integrin to the cell surface vascular endothelial growth factor and type I collagen inducible protein, thereby treating the patient with the pathological condition caused by the integrin-mediated cell-cell interaction.

Claim 33 is canceled and its limitation is incorporated in claim 32, which is amended to overcome the 35 U.S.C. §112, first paragraph (enablement and written description requirement) and the 35 U.S.C. §103 rejections. Amended claim 33 is directed to a method of inhibiting angiogenesis and the formation of capillaries in a patient in need of such a treatment. This method comprises administering to the patient a pharmacologically effective amount of antibody directed against a peptide with a sequence of SEQ ID No. 41 or SEQ ID No. 2 that is derived from vascular endothelial growth factor and type I collagen inducible protein (VCIP), where the antibody inhibits integrin-mediated cell-cell interaction, thereby inhibiting angiogenesis and the formation of capillaries in the patient in need of such a treatment.

Claims 14, 20 and 21 that recite limitations of independent claims 8 or 15 are amended by canceling non-elected inventions and the Markush language. Amended claims 14 and 20 limit the cell-cell interaction recited in claims 8 and 15, respectively, to inflammation, angiogenesis or a combination thereof. Amended claim 21 limits the pathological condition recited in claim 15 to tumor growth, inflammation, angiogenesis or a combination thereof.

Amendment to the Specification

The specification is amended to include the sequence identifier for the sequences in Figures 1L, IM and 14H.

Amendment to the Drawings

Additionally, the drawings for Figure 1L and 14H are amended to include the sequence identifier. Please replace the sheet for Figure 1L and 14A-H with the enclosed sheets.

Amendment to the Sequence Listing

Applicant encloses a computer readable form of Sequence Listing that includes SEQ ID No. 42 and a paper copy of the same along with this response.

Objections to the Specification under 37 C.F.R. 1.821(d)

The Examiner has objected to the specification for failing to provide a sequence identifier for each individual sequence in Figures 1L, 1M and 14H (pages 6 and 13, respectively) and in Table 1 (page 34).

Applicant has amended the specification by identifying the sequence in figures 1L, 1M and 14H. Additionally, Applicant has also amended the drawings for figures 1L and 14H to include the SEQ ID Nos. for the sequences. Furthermore, the sequence listing has been amended to include the sequence identifed in Fig. 14H.

With regard to the identification of sequences in Table 1, Applicant submits that Table 1 was amended in the response mailed August 18, 2005 to include SEQ ID Nos. for the sequences of the peptides (SEQ ID Nos. 20 and 21) listed in the table. The anti-rabbit IgG antibody listed in the table is a commercially available antibody and therefore the sequence of this antibody is not identified in this table. Further, with regard to the identification of sequence of anti-VCIP-RGD antibody in Table 1, Applicant would like to respectfully point out that the instant specification teaches that this antibody was raised using peptide of SEQ ID No. 2 that was synthesized commercially (page 21, lines 25-28). Based on this teaching, one of ordinary skill in the art can easily raise anti-VCIP-RGD antibody using this peptide in techniques that are routine in the art. Thus, Applicant contends that it is not necessary to identify the sequence of anti-VCIP-RGD antibody in Table 1. Accordingly, based on amendments and above-mentioned remarks, Applicant respectfully requests the withdrawal of objections to the specification.

The 35 U.S.C. §112, Second Paragraph, Rejection

Claims 8-9 and 14 stand rejected under 35 U.S.C. §112, second paragraph for being indefinite. Applicant respectfully traverses this rejection.

The Examiner states that claim 8 is incomplete for omitting essential steps, i.e., the step of contacting the cells with the reagents that block the binding of integrins to cell surface VCIP.

Claim 8 is amended and Applicant contends that amended claim 8 clearly and accurately describes the invention and how it is practiced. Accordingly, based on the claim amendment and above-mentioned remarks, Applicant respectfully requests the withdrawal of rejection of claims 8-9 and 14 under 35 U.S.C. §112, second paragraph.

The 35 U.S.C. §112, First Paragraph Rejection

Claims 8-11, 14-17, 20-21 and 32-33 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicant respectfully traverses this rejection.

The Examiner states that the instant specification does not provide enablement for the claims as they are written. The Examiner further states that the specification disclosure is insufficient to enable one skilled in the art to practice the broadly claimed invention without undue experimentation. The Examiner cites references such as **Fogarty M.**, **Wallace R.W.** and **Fan** *et al* to demonstrate unpredictability in the art directed to methods of inhibiting cell-cell interaction/angiogenesis and thus the specification has to provide specific enablement to satisfy the statue. The Examiner further states that since the claimed method has not been practiced in an animal model and the specification does not disclose how to inhibit angiogenesis or reach a therapeutic endpoint in humans by administering the anti-CRGDD antibodies, it is not clear whether the *in vitro* studies clearly reflect the efficacy of the claimed therapeutic strategy in humans.

Furthermore, the Examiner states that since the treatment using any agent that blocks the binding of integrin via VCIP is not yet known, the disclosure of mechanisms mediating cell-cell interaction does not provide sufficient guidelines to a method of angiogenesis treatment *in vivo*. While pointing to the claim language, the Examiner states the use of terms "has" and "comprise" in claims 10, 11, 16, 17 and 32-33 makes the claims open ended and extend the CRGDD peptides to include additional non-specified amino acids on either or both C or N-terminals of SEQ ID Nos. 41 or 2. The use of this language also makes the antibody that binds to the epitope unpredictable. Thus, the Examiner concludes that without detailed direction as to which agents are essential to the function of VCIP, a person of skill in art would not be able to determine without undue experimentation which of the plethora of agents encompassed by the instant claims would share the ability to inhibit cell-cell interaction/angiogenesis mediated by VCIP.

Independent claims 8, 15 and 32 are amended as discussed supra. Claims 10, 11, 16, 17 and 32 are canceled. The antibody used in the method claims 8, 15 and 32 is directed against peptides having specific sequences such as SEQ ID No. 41 or SEQ ID No. 2 that are derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP). Thus, the claim language in amended claims 8, 15 and 32 is not open-ended. The instant invention discloses that VCIP is involved in cell-cell interaction, intracellular signaling and in the development of pathophysiological states. To this effect, the instant specification teaches that the VCIP sequence comprises a RGD motif which enables VCIP to act as an integrin ligand and promotes cell-cell interactions and intracellular signaling.

The instant invention further teaches that incubation of cells (HEK293) expressing wild type VCIP with peptides that comprised RGD motif or with anti-VCIP-RGD antibody generated using the peptide of SEQ ID No. 2, inhibited cell-cell interaction (Example 14; Table 1). Investigation of the mechanism contributing cell-cell interaction in the above-mentioned cells demonstrated that the cell-cell interaction was integrin mediated and that VCIP-RGD acted as a cell-

associated integrin ligand (Example 15-18). The instant invention also investigated the contribution of VCIP-RGD in adhesion of endothelial cells to extracellular matrix (Example 19). With regards to angiogenesis, the highly motile behaviour of activated endothelial cells is known in the art to be crucial for angiogenesis. Since sprouting of new blood vessels requires cell division in preformed endothelial tissues (for instance, wall of the blood vessel) that is accompanied by migration of the endothelial cells, unnecessary angiogenesis can be prevented by inhibiting the migratory behavior of the endothelial cells (page 40, lines 25-30). The instant invention examined the role played by VCIP in the endothelial cell migration and angiogenesis by performing *in vitro* assays (Example 21-26) that are considered in the art to correlate with the results that one might expect to see *in vivo*. Mouse model (in vivo) was used to demonstrate that VCIP potentiated tumor growth by promoting tumor angiogenesis and augmented tumor metastasis (Examples 27-29). The instant invention demonstrated that anti-VCIP antibody blocked angiogenesis by inhibiting the formation of new capillaries *in vitro* (Example 29).

With regards to Examiner's citation of prior art to demonstrate unpredictability directed to methods of inhibiting cell-cell interaction/angiogenesis, Applicant would like to respectfully point out that although some inhibitors of angiogenesis failed, the search for more of such inhibitors has not ceased since the time these references were published. In fact, some of these drugs have been approved by Food and Drug administration in the treatment of cancer (Antiangiogenic Therapeutic Approaches to Treating Cancer: The perspective in 2004). Thus, Applicant submits that the instant specification provides ample teaching as discussed above regarding the utility of the antibody directed against the peptides with SEQ ID No. 41 or 2 in the inhibition of cell-cell interaction to satisfy the statue.

Furthermore, with regard to the absence of *in vivo* testing of the inhibitor and lack of disclosure in the specification regarding the therapeutic endpoint of this drug, Applicant submits that examination of an anti-angiogenic drug for its therapeutic efficacy is not new in the art. As discussed in the instant

specification, growth of tumors beyond 2-3 mm in size requires formation of their own blood supply. Upon vascularization, dormant tumors grow and eventually form metastatic foci at distant site. The instant specification teaches that anti-VCIP antibody inhibited cell-cell interaction. Further, the instant invention using xenograft experiments demonstrated that tumor cells expressing VCIP grew dramatically with distinct vasculature as opposed to tumors lacking such expression or expressing mutant VCIP (Example 27). Additionally, VCIP was also shown to augment tumor metastasis (Example 28). Thus, by demonstrating that the anti-VCIP antibody inhibited the formation of new capillaries in vitro, the instant invention has disclosed the therapeutic endpoint of these antibodies. Further, Applicant respectfully disagrees with the Examiner's statement that since an agent that blocks the binding the integrin via VCIP is not yet known, the disclosure of mechanisms mediating cell-cell interaction does not provide sufficient guidance to a method of angiogenesis treatment *in vivo* for the reason discussed supra.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with the information known in the art without undue experimentation (M.P.E.P. 2164.01). Based on the *in vivo* effects of VCIP and the in vitro effects of anti-VCIP antibody directed to peptides having RGD sequence, the Applicant submits that the instant invention has provided sufficient enablement to use the anti-VCIP antibody in the claimed method without undue experimentation. Thus, the scope of the claimed invention is commensurate with the scope of enablement provided. Accordingly, based on the claim amendments and remarks, Applicant respectfully request the withdrawal of rejection of claims 8-11, 14-17, 20-21 and 32-33 under 35 U.S.C. §112, first paragraph.

Claims 8-11, 14-17, 20-21 and 32-33 are rejected under 35 U.S.C. §112, first paragraph rejection for not complying with the written description requirement. Applicant respectfully traverses this rejection.

The Examiner states that the Applicant is in possession of an in vitro method of inhibiting cell-cell interaction with the antibody that binds a peptide

consisting of SEQ ID NO: 2 but not of the method as claimed. The Examiner further states that the specification's disclosure is inadequate to describe the claimed genus of agents. Additionally, the Examiner states that the Applicant has disclosed only amino acid of SEQ ID NO: 41 and 2, therefore the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Thus, the Examiner concludes that the specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.

As discussed *supra*, Applicant has amended claims 8, 15 and 32 to recite a method utilizing the antibody directed against peptide with sequence of SEQ I D No. 41 or SEQ ID No. 2. Since the amended claims recite specific amino acid sequences that are disclosed in the instant specification, they enable one of ordinary skill in the art to recognize the subject matter that is claimed, thereby complying with the written description requirement. Accordingly, based on the amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 8-11, 14-17, 20-21 and 32-33 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §102 Rejections

Claims 8-11 and 14 are rejected under 35 U.S.C. §102(b) as being anticipated by **Vassilev** *et al* (Blood 1999 Jun 1; 93(11):3624-3631) as evidenced by **Bendayan** (J Histochem Cytochem 1995, 43:881-886). Applicant traverses this rejection.

The Examiner describes the following teachings of **Vassilev** *et al*: (1) a method of inhibiting platelet aggregation "cell-cell interaction" by anti-RGD antibodies (page 3626, 1st col., 2nd para and Fig. 4) and (2) RGD motif plays a central role in mediating cell-cell adhesion in a variety of immunological and inflammatory processes. For instance, cyclic RGD peptides have shown to inhibit $\alpha 4\beta 1$-dependent adhesion of T cells to cytokine activated endothelial cells (page 3629, 1st col., last para to 2nd col., 1st para). Since antibodies cross-react with

antigens having homologous amino acid residues, the Examiner concludes that the reference anti-RGD antibody would bind to the peptide comprising SEQ ID NO: 41 and 2 due to shared sequence homology.

The Examiner states that the above-discussed conclusion is true since **Bendayan** who characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin shows that although the antibody is highly specific, it is able to bind not only to human proinsulin but to proinsulin from other species and even a distinct protein, glucagons based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (entire document). Specifically, the Examiner points out the conclusion by **Bendayan** that "an antibody directed against such sequence, although still yielding specific labeling could reveal different molecules not related to original antigen" (pg 886, last para). Based on this, the Examiner states that although the prior art references do not teach of blocking the binding of integrins to cell surface VCIP per se, the method and the product used in the reference method are the same as the claimed method. Therefore, the Examiner considers "blocking of integrins to cell surface VCIP" to be inherent and concludes that the reference teachings anticipate the claimed method.

Amended claim 8 recites an antibody directed against a peptide with specific sequences such as SEQ ID No. 41 or SEQ ID No. 2 that is derived from VCIP. Contacting the cells with such an antibody blocks binding of integrins to VCIP, thereby inhibiting the cell-cell interaction. **Vassilev** *et al* teach that the antibody was directed against a 10-amino acid peptide containing the RGD motif (page 3624, 2nd col., last para). Vassilev et al neither teach that the antibody was directed against the 5-amino acid peptide (SEQ ID No. 41) or 20 amino acid peptide (SEQ ID No. 2) nor does it teach that the peptide was derived from VCIP as disclosed by the instant invention (see discussion supra). Therefore, **Vassilev** *et al* does not teach each and every element of the claim. Furthermore, since **Vassilev** *et al* do not teach the above-discussed elements of the claim, the product used in the reference method is not the same as the claimed method. Therefore, whether an antibody generated using the above-mentioned peptides would block the

binding of integrins to cell surface VCIP is not inherent. Hence, independent claim 8 and its dependent claims 9 and 14 are not anticipated by **Vassilev** *et al.* Accordingly, based on the claim amendments and above-discussed remarks, Applicant respectfully requests the withdrawal of rejection of claims 8-11 and 14 under 35 U.S.C. 102(b).

Claims 15 and 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by **U.S. Patent No. 5, 807,819**. Applicant respectfully traverses this rejection.

The Examiner cites the following teachings of **U.S. Patent No. 5,807,819**: (1) a method of treating angiogenesis comprising administering to the subject RGD-containing peptides (abstract and entire document), and (2) angiogenesis is required for the growth of solid tumors and neovascularization serves as a conduit for metastasis (col. 9, lines 19-21). The Examiner further states that although the prior art does not teach of blocking the binding of integrins to cell surface VCIP per se, the method and the product used in the reference method are the same as the claimed method. Therefore, the Examiner considers "blocks the binding of integrins to cell surface VCIP" as inherent. Thus, the Examiner concludes that the reference teachings anticipate the claimed invention.

Claim 15 is amended to recite a method of treating a patient with a pathological condition caused by integrin-mediated cell-cell interaction comprising administering to the patient an antibody directed against a peptide with a sequence of SEQ ID NO. 41 or SEQ ID No. 2 that is derived from VCIP. Such an antibody blocks binding of integrin to the cell surface VCIP, thus treating the patient with the pathological condition. **U.S. Patent No. 5,807,819** does not teach a method of treatment that comprises administration of an antibody directed against the specific VCIP derived peptides. Hence, **U.S. Patent No. 5,807,819** does not teach each and every element of the claimed invention. Furthermore, since the product used in the reference method is not the same as the claimed invention, "blocks the binding of integrin to cell surface VCIP" is not inherent. Hence, independent claim 15 and

its dependent claims 20 and 21 is not anticipated by **U.S. Patent No. 5,807,819.** Accordingly, based on claim amendments and above-discussed remarks, Applicant respectfully requests the withdrawal of rejection of claims 15 and 20-21 under 35 U.S.C. §102(b).

The 35 U.S.C. §103 Rejection

Claims 15-17 and 20-33 are rejected under 35 U.S.C 103(a) as being unpatentable over **U.S. Patent No. 5,807,819** in view of **U.S. Patent No. 5,567,440** and **Vassilev** *et al* as is evidenced by **Bendayan**. Applicant respectfully traverses this rejection.

The Examiner states that **U.S. Patent No. 5,807,819** also teaches methods of using the Arg-Gly-Asp containing peptides such as CRGDDVC (patented SEQ ID NO: 17) to alter $\alpha v\beta 3$ integrin receptor-mediated binding of a endothelial cell to a matrix. Additionally, the Examiner states that **U.S. Patent No. 5,807,819** teaches methods for ameliorating the severity of a pathology characterized by an undesirable level of angiogenesis in a subject using RGD-containing peptides.

With regards to the **U.S. Patent No. 5,567,440,** the Examiner states that the patent teaches that cell adhesion plays an important role in human disease and that these interactions proceed by the interaction of receptors on the surface of a cell with proteins or glycosaminoglycans on the surface of another cell or within the extracellular matrix. The Examiner further states that the **U.S. Patent No. 5,567,440** also teaches that routes to the interruption of these interactions typically involve competitive inhibition of these receptor-ligand interactions, for example, with antibodies, soluble ligands which act as receptor antagonists (e.g. cyclic RGD peptides), soluble receptors or other competitors (col. 1, lines 17-30).

Based on the discussion above, the Examiner considers the limitation "blocks the binding of integrins to cell surface VCIP" to be expected as a result of the method. Thus, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the

CRGDDVC cyclic peptide taught by **U.S. Patent No. 5,807,819** with anti-RGD antibody taught by **Vassilev** *et al* in a method of inhibiting angiogenesis in a subject. The Examiner further states that one of ordinary skill in the art at the time the invention was made would have been motivated to do so because routes to interruption of cell-cell interactions typically involve competitive inhibition of these receptor ligand interactions with either receptor antagonists e.g. cyclic RGD peptides, antibodies or other competitors. Furthermore, the Examiner states that based on the combined teachings of the references, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Thus, the Examiner concludes that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made as evidenced by the references and in the absence of the contrary.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine the teachings. Second, there must be reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations (M.P.E.P. 2143).

Claim 15 recites a method of treatment that uses an antibody directed against specific VCIP-derived peptides (SEQ ID No. 41 or SEQ ID No. 2). Claim 32 is amended to recite a method of inhibiting angiogenesis and formation of capillaries in a patient comprising administering to the patient an antibody directed against specific VCIP-derived peptides (SEQ ID No. 41 or SEQ ID No. 2). The anti-RGD antibody generated in **Vassilev** *et al* is directed against a 10-amino acid peptide and not the specific VCIP-derived peptide as taught by the instant invention. Therefore, the prior art references combined do not teach or suggest all the limitations of the instant claim nor do they motivate one of ordinary skill in the art to arrive at the instant invention with reasonable expectation of success. Accordingly based on the claim amendments and above-mentioned remarks,

Applicant respectfully requests the withdrawal of rejection of claims 15-17 and 20-33 under 35 U.S.C §103(a).

This is intended to be a complete response to the Office Action mailed September 30, 2005. Applicant submits that the pending claims are in condition for allowance.

Respectfully submitted

Date: Jan 11, 2006

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com

AMENDMENTS TO THE DRAWINGS

Please replace the Drawings for Figures IL and 14A-H originally mailed on March 29, 2004 with the enclosed Drawings.